Medical and Pediatric Oncology 27:515–520 (1996)

Evaluation of Patients With Advanced Neuroblastoma Surviving More Than 5 Years After Initiation of an Intensive Japanese Protocol: A Report From the Study Group of Japan for Treatment of Advanced Neuroblastoma

Makoto Iwafuchi, MD, Jiro Utsumi, MD, Yoshiaki Tsuchida, MD, Michio Kaneko, MD, Shiro Matsuyama, MD, Naomi Ohnuma, MD, Nobuyuki Taguchi, MD, Hideo Mugishima, MD, Jotaro Yokoyama, MD, Shingi Sasaki, MD, Akira Yoshioka, MD, Noboru Nagahara, MD, Masahiro Fukuzawa, MD, and Sachiyo Suita, MD

In January 1985, a single protocol consisting of cyclophosphamide, vincristine, tetrahydropyranyl adriamycin, and cis-platinum for the treatment of advanced neuroblastoma was begun nationwide in Japan and was found to improve clinical results significantly in terms of 2- or 3-year survival rate.

Between January 1985 and December 1988, 113 eligible patients (7 infants younger than 12 months of age with stage IVA disease and 106 patients aged 12 months or older with stage III or IV disease) were enrolled and followed up for 5 years or more after initiation of treatment, as of March 1994. In this study, the usefulness of the protocol for the treatment of advanced neuroblastoma was evaluated with survival rates in relation to age, tumor site, stage, and N-myc amplification for patients surviving more than 5 years after initiation of the protocol. Fifty of the 113 patients were alive 5 years or more after initiation of the treatment, 39 without any episodes of disease recurrence. Fourteen (70%) of 20 patients with stage III, 6 (50%) of 12 with stage IVB, and 24 (30%) of 81 with stage IVA disease were alive and disease-free 5 years after initiation of the protocol. Twenty (56%) of 36 patients without N-myc amplification were alive at 5 years after initiation of the protocol. Only one patient who was alive without evidence of the disease at 5 years had recurrence afterward.

Key words: advanced neuroblastoma, survival rate, intensive induction chemotherapy, surgery

INTRODUCTION

A nationwide intensive protocol for the treatment of advanced neuroblastomas begun in January 1985 was found by the Study Group of Japan to have improved clinical results significantly (survival rates were 77% in stage III and 54.3% in stage IV at 2 years, and 70% in stage III and 45% in stage IV at 3 years) [1].

It was also reported [2–5] that gross complete resection of a primary tumor and lymph nodes has a significant value in achieving complete remission and survival in patients with advanced neuroblastoma, when it was done together with very intensive induction chemotherapy, as recommended in the Japanese protocol [1,2].

In this study, the efficacy of the intensive Japanese protocol for the treatment of advanced neuroblastoma is evaluated with regard to age at diagnosis, tumor site, and stage at diagnosis in patients surviving more than 5 years after initiation of the treatment.

PATIENTS AND METHODS

Patients with neuroblastoma were classified according to the Japanese staging system [6], which is similar to the staging system of the Children's Cancer Group (CCG) [7] except that it subdivides stage IV into stages IVA and IVB (Table I).

Evaluation was undertaken on 113 eligible patients consisting of 7 infants younger than 12 months of age with stage IVA disease (bone cortex, distant lymph nodes, and/or remote organ metastases) [6] and 106 patients aged 12 months or older with stage III or IV disease (IVA plus IVB with original tumor crossing over the abdominal midline and with metastases confined to the bone marrow, liver, and skin).

The patients first received a 6-cycle course of chemotherapy (regimen A_1), consisting of cyclophosphamide

From the Study Group of Japan for Treatment of Advanced Neuroblastoma, Tokyo and Tsukuba, Japan.

Received February 22, 1995; accepted December 19, 1995.

Address reprint requests to Dr. Makoto Iwafuchi, Department of Pediatric Surgery, School of Medicine, Niigata University, 1-757 Asahimachi-Dohri, Niigata 951, Japan.

Presented in part at the 26th Meeting of the International Society of Paediatric Oncology, Paris, September 20–24, 1994.

TABLE I. Staging System of Neuroblastoma in Japan [6]

Stage I	Similar to that of the Children's Cancer Group [7]
Stage II	Similar to that of the Children's Cancer Group [7]
Stage III	Similar to that of the Children's Cancer Group [7]
Stage IVA	Patients with bone cortex, distant lymph node, and/or remote organ metastases
Stage IVB	Patients whose original tumors are stage III but who have metastases confined to the liver, skin, and bone marrow
Stage IVS	Similar to that of the Children's Cancer Group [7]

1,200 mg/m^2 continuous infusion over 6 hr and vincristine 1.5 mg/m^2 on day 1, tetrahydropyranyl (THP)-adriamycin (pyrarubicin or THP-adriamycin; Sanraku Ocean Co., Tokyo, Japan) 40 mg/m^2 on day 3, and cis-platinum 90 mg/m^2 on day 5. This regimen A_1 was repeated every 4 weeks [1,2]. Resection of primary tumors and regional lymph node metastases was performed after 3–6 cycles of regimen A_1, when the surgeons found the resection would be feasible.

After 6 cycles of the initial chemotherapy and surgery, the patients were further divided into two groups: a continuous chemotherapy group and a bone marrow transplantation (BMT) group. Patients in the continuous chemotherapy group were subdivided into courses 1 and 2 according to type of drug administration. In course 1, patients were treated with alternate administration of regimen B and intensified regimen A_1 (regimen A_2) for 7 cycles. Regimen B consisted of cyclophosphamide 1,500 mg/m^2 on day 1 and 3-[(4-amino-2-methyl-5-pyrimidinyl) methyl]-1-(2-chloroethyl)-1-nitrosourea (ACNU; Sankyo Co., Tokyo, Japan) 100 mg/m^2 on day 3, and regimen A_2 consisted of cyclophosphamide 1,500 mg/m^2 on day 1, pyrarubicin 50 mg/m^2 on day 3, and cis-platinum 90 mg/m^2 on day 5. Regimen A_2 was given 6 weeks after regimen B and was changed back to regimen B after 4 weeks. In course 2, patients were treated with alternate administration of regimen C and regimen A_2 for 7 cycles every 4 weeks. Regimen C consisted of cyclophosphamide 1,500 mg/m^2 on day 1 and dacarbazin (DTIC) 250 mg/m^2 on days 1–5. Patients in the BMT group underwent an autologous bone marrow transplantation, preconditioned by melphalan (L-PAM) as the main drug or by the combination of melphalan, cis-platinum, etoposide, and others, with or without total body irradiation. (See ref. [8] for treatment schema.) The decision to allocate the patients to one of the three courses was made by the institution. Patients who received chemotherapy a little longer (for an additional 3–6 months) were judged eligible for the study.

Statistical analysis was performed using the chi-square test, Cochran-Armitage's trend test, and Fisher's exact method.

RESULTS

Between January 1985 and December 1988, 142 patients were entered in this study. However, 20 cases were treated with another protocol before entering this study and in 9 cases the treatment violated the original treatment protocols of the Study Group of Japan. Therefore, the results of treatment of 113 newly treated patients were analyzed. All 113 cases were found to be eligible for the study.

Course 1 was applied to only 12 patients because of prolonged myelosuppression attributed to ACNU. Seventy-four cases were further treated with the protocol of course 2 and 27 patients (9 stage III and 18 stage IV) were treated with BMT (course 3).

All results were evaluated as of March 1994. There were no losses of the patients to follow-up. Fifty (44%) of 113 patients enrolled between January 1985 and December 1988 were alive 5 years after initiation of this protocol. Thirty-nine patients (35%) were alive without any evidence of the disease throughout the clinical course (event-free survivors). Of these 50 patients, 11 had had recurrence within 5 years or recurrence afterward: 2 within 3 years, 8 between 3 and 5 years, and 1 after 5 years. Finally, 5 of the 11 patients with recurrence had recovered and survived disease-free (bringing the number of disease-free survivors to 44); 4 were alive with the disease at 5 years and the remaining 2 died after 5 years. Sixty-three patients were dead before 5 years after administration of the treatment: 49 died of disease progression and 14 of unrelated causes.

Survivals were evaluated in relation to prognostic factors.

Age

Eleven (37%) of 30 patients aged 1 year or younger at diagnosis, 26 (46%) of 56 aged 2–4 years, and 13 (48%) of 27 aged 5 years or older were alive 5 years after initiation of the protocol. Event-free 5-year survival rates were 37%, 34%, and 33%, respectively; there was no statistically significant difference in survival rates between these groups (Table II).

Tumor Site

Nine (64%) of 14 patients with tumors originating in the thorax and 41 (41%) of 99 patients with tumors in the abdomen were alive 5 years after initiation of the protocol. Event-free 5-year survival rates were 57% and 31%, respectively. No statistically significant difference in survival rates between the former and latter groups was noted (Table III).

Stage

Fifteen (75%) of 20 patients with stage III, 6 (50%) of 12 with stage IVB, and 29 (36%) of 81 with stage

TABLE II. Survival at 5 Years According to Age at Diagnosis*

Age at diagnosis	No. of cases	Overall survival	Event-free survival
≤1 year[a]	30[a]	11 (37 ± 7%)	11 (37 ± 7%)
2–4 years	56	26 (46 ± 5%)	19 (34 ± 5%)
≥5 years	27	13 (48 ± 8%)	9 (33 ± 7%)
Total	113	50 (44 ± 4%)	39 (35 ± 3%)

*Standard errors of the survival rates are given. No statistically significant difference was noted among the groups.
[a]Seven patients were younger than 12 months.

TABLE III. Survival at 5 Years According to Original Site*

Site	No. of cases	Overall survival	Event-free survival
Thorax	14	9 (64 ± 12%)	8 (57 ± 12%)
Abdomen	99	41 (41 ± 4%)	31 (31 ± 4%)
Total	113	50 (44 ± 4%)	39 (35 ± 3%)

*Standard errors of the survival rates are given. No statistically significant difference was noted among the groups. Statistical analysis was by chi-square test.

IVA disease were alive 5 years after initiation of the protocol. Similarly, 14 patients with stage III, 6 with stage IVB, and 24 with stage IVA were alive and disease-free 5 years after initiation of the protocol.

Event-free 5-year survival rates were 65% in stage III, 42% in stage IVB, and 26% in stage IVA. Differences in survival rates among stages III, IVB, and IVA were statistically significant ($P < 0.01$) (Table IV).

Only 1 (No. 16, stage IVA in Fig. 1) of 40 patients who was alive without evidence of the disease 5 years after initiation of the protocol had a recurrence after 5 years. However, this patient subsequently became disease-free.

N-myc Amplification

Twenty (56%) of 36 patients without N-myc amplification (less than 10 copies) were alive, while only 4 (25%) of 16 with N-myc amplification (more than 10 copies) were alive 5 years after initiation of the protocol. Event-free 5-year survival rates were 39% (14 of 36 cases) and 13% (2 of 16 cases), respectively (Table V). A significant difference in survival rates between the former and the latter groups was statistically noted ($P < 0.05$).

Treatment Modalities

Courses 1 and 2 (continuation chemotherapy) were applied to 12 and 74 patients, respectively, while 27 patients (9 stage III, 18 stage IV) were further treated with BMT (course 3). Among the 27 patients, 3 received purged and 23 received unpurged autologous marrow, while 1 case was treated with allogenic BMT. No patients

TABLE IV. Survival at 5 Years According to Clinical Stage†

Clinical stage	No. of cases	Overall survival	Event-free survival
Stage III	20	15 (75 ± 9%)*	13 (65 ± 10%)**
Stage IVB	12	6 (50 ± 12%)*	5 (42 ± 11%)**
Stage IVA	81	29 (36 ± 4%)*	21 (26 ± 3%)**
Total	113	50 (44 ± 4%)	39 (35 ± 3%)

†Standard errors of the survival rates are given.
*$P < 0.05$; **$P < 0.01$. Statistical analysis was by Cochran-Armitage's trend test.

were treated with unpurged peripheral blood stem cells. Patients were allotted to each arm not on the basis of true randomization.

No significant difference was found in the survival rates between patients treated with BMT and those achieving complete remission but not undergoing BMT. The results were recently reported in detail elsewhere [8].

The clinical course of a representative case is presented below.

Case 1. This was a 4-year-old girl with stage III neuroblastoma originating in the left adrenal gland (No. 9, stage III in Fig. 1). She was treated by 5-cycle administration of regimen A_1, and also operated on, before she underwent autologous bone marrow transplantation (ABMT), preconditioned by melphalan (180 mg/m^2). After ABMT, a bone metastasis was found by bone scintigraphy in the right tibia, and she was further treated intensively, including local irradiation to the bone metastasis. During the course of the subsequent chemotherapy no metastasis was seen, and the patient is healthy with no evidence of disease 7 years and 6 months after the initiation of treatment.

DISCUSSION

The clinical outcome for patients with stage IV neuroblastoma was considered dismal before 1980 [4], but has been improving in recent years due to the active introduction of intensive induction chemotherapy [1,3, 9,10]. In addition, advances in operative techniques [11] and increased surgical resectability due to intensive induction chemotherapy have been helpful in improving the rate of complete remission in advanced neuroblastoma. Several articles have reported that the survival rates of patients with advanced neuroblastoma were improved 2 or 3 years after initiation of the treatment [1,3,4].

However, there are very few reports of 5-year long-term survivors of advanced neuroblastoma, and this may be the first chance to review all 44 disease-free survivors at 5 years. First of all, it is important to note that there are 5 patients among the 44 who had one recurrence but recovered and eventually became disease-free (Fig. 1), e.g., in the clinical course of case 1. This leads to the conclusion that intensive management should be encour-

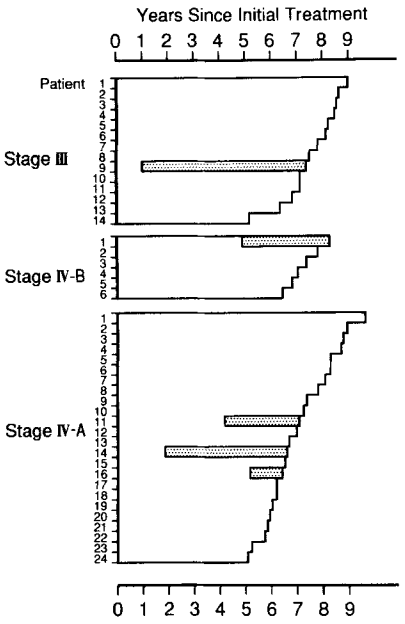

Fig. 1. Disease-free 5-year survival for 44 patients with advanced neuroblastoma: 14 in stage III, 6 in stage IVB, and 24 in stage IVA. Event-free 5-year survival for 39: 13 in stage III, 5 in stage IVB, and 21 in stage IVA. Event-free survival (□, n = 39); recurrence but now disease-free (▨, n = 5).

TABLE V. Survival at 5 Years According to Degree of N-myc Amplification†

N-myc amplification	No. of cases	Overall survival	Event-free survival
<10 copies	36	20 (56 ± 7%)*	14 (39 ± 6%)**
≥10 copies	16	4 (25 ± 7%)*	2 (13 ± 4%)**

†Standard errors of the survival rates are given.
*$P < 0.05$; **$P < 0.01$. Statistical analysis was by Fisher's exact method.

aged even after what is thought to be recurrence happens in the clinical course of advanced neuroblastomas.

The overall 5-year survival rate for all patients (stages III and IV) was 44%, and the event-free 5-year survival rate was 35%. These figures are better than were expected at the start of our group study in 1985. As mentioned earlier, the high survival rate observed during this study might be due in large part to the effectiveness of our intensive induction chemotherapy, and also possibly to our positive attitude toward surgical resection [2].

In regard to the relationship between age and survival, Paul and colleagues [10] reported that actuarial event-free survival at 5 years for 24 patients younger than 12 months of age with stage IV neuroblastoma was 75%. The value is not necessarily surprising, because infants younger than 12 months with stage IV neuroblastoma have a very good prognosis if pseudo-IVS patients without bone cortex metastases—the Japanese stage IVB patients (Table I)—are included. Whether infants younger than 12 months of age with stage IVA disease do better or worse is a longstanding question because of the relatively small number of patients worldwide. In the present study, results at 5 years for 7 infants younger than 12 months with stage IVA disease were analyzed together with a group of stage III, IVB, and IVA patients aged 13–24 months. All of the 7 infants were older than 7 months at diagnosis; 3 of the 7 patients survived event-free for more than 5 years, 3 died of disease, and 1 died of pneumonia and sepsis within 1 month after diagnosis. The event-free survival rate for them at 5 years was 43%, which was a little better than the event-free 5-year survival rate for patients aged 2 years or more and different from previous reports [9,12,13]. It should be remembered that all of our stage IV patients younger than 12 months had stage IVA disease and that we did not include any stage IVB infants younger than 12 months who had a better prognosis [6].

In regard to the relationship between tumor site and survival, Grosfeld and coworkers [13] reported that tumor site did not influence surgical outcome to any great degree. In our series, patients with tumors originating in the thorax appeared to have a better prognosis (Table III). However, there was statistically no significant difference between these two groups with different sites of origin.

In regard to the relationship between stage and survival, event-free 5-year survival rates were 65% in stage III, 42% in stage IVB, and 26% in stage IVA in the present series. Several reports [2,14,15] showed, without disagreement among authors, that survival rates in patients with regional lesions (stage III) were better when the tumor was completely excised. On the other hand, long-term survival rates for patients with stage IV, especially stage IVA, are not yet satisfactory. Concerning the treatment of stage IV neuroblastomas, Matsumura and colleagues [9] reported from the CCG of the United States that the chemotherapeutic resolution of metastases had a greater impact on subsequent length of survival than resectability at delayed surgical procedure. Berthold and coworkers [16] thought that preoperative chemotherapy might be one of the effective tools for surgery to achieve complete removal of initially unresectable primary tumors and metastases.

The fact that only one patient who was without evidence of disease at 5 years showed recurrence afterward may confirm that patients surviving for 5 years without disease have very little chance of recurrence (Fig. 2) and that the time point of 5 years is a suitable one for analysis of the follow-up of patients with advanced neuroblastomas. This patient was not included in the group of 39 event-free survivors in the present analysis, because of the too short observation after recurrence at the present

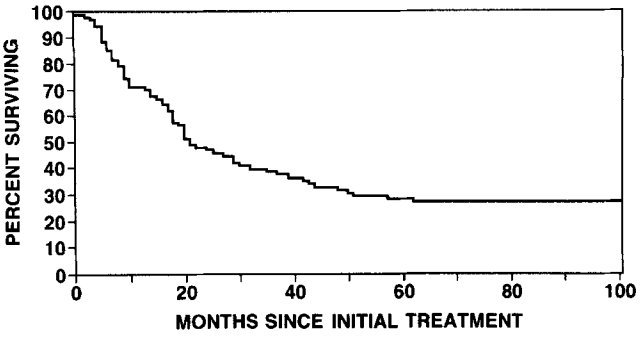

Fig. 2. Event-free survival curve of 86 patients with stage IV disease who are older than 12 months of age at initiation of treatment. One showed recurrence after 5 years.

moment even though the patient again became disease-free.

In regard to the relationship between N-myc amplification and survival, the event-free 5-year survival rate was 56% for patients without amplification, while it was 19% for those with amplified tumors. The difference was statistically significant in the present analysis ($P < 0.05$). Because of the small number of cases, the survival rate for amplified tumors was lower in the present study, but a recent study of ours [17] found an actuarial survival rate at 5 years for amplified neuroblastomas of 43.5%.

CONCLUSIONS

The Japanese protocol for treatment of advanced neuroblastoma significantly improved the clinical results:

1. Thirty-nine (35%) of 113 eligible patients with advanced neuroblastoma survived event-free and 44 (39%) were disease-free 5 years after initiation of the treatment.
2. Only 1 of 40 patients who were alive and event-free at 5 years had recurrence afterward.
3. The results, however, await further confirmation with larger numbers of patients.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions and support of Prof. Jun-ichi Uchino, Sapporo, Prof. Hideyo Takahashi, Chiba, Dr. Yasutaka Hoshi, Tokyo, Dr. Mutsuro Ohira, Tokyo, Prof. Ikuo Okabe, Tokyo, Dr. Hirokazu Nishihira, Yokohama, Prof. Akira Okada, Osaka, and Dr. Keisei Kawa, Izumi.

Other members of the Study Group of Japan for Treatment of Advanced Neuroblastoma are Dr. T. Takeda, Dr. H. Kenmotsu, Dr. S. Makino, Dr. T. Fujisawa, Dr. T. Honna, Dr. A. Hayashi, Dr. T. Nishina, Dr. K. Nakada, Prof. S. Yokoyama, Dr. K. Ishida, Dr. K. Takano, Dr. Y. Tsukahara, Prof. M. Sakurai, Prof. T. Sawada, Prof. A. Toyosaka, Prof. H. Ueda, Prof. Y. Sera, Dr. H. Tasaka, and Prof. H. Takamatsu.

The authors also thank Ms. Susan Schmidt and Ms. E. Yoshida for their kind assistance in manuscript preparation.

This work was supported in part by the Grant-in-Aid for Cancer Research (5-16) from the Ministry of Health and Welfare of the Government of Japan.

REFERENCES

1. Sawaguchi S, Kaneko M, Uchino J, Takeda T, Iwafuchi M, Matsuyama S, Takahashi N, Nakajo T, Hoshi Y, Okabe I, Yokoyama J, Nishihira H, Sasaki S, Sakurai M, Sawada T, Nagahara N, Tsuchida Y: Treatment of advanced neuroblastoma with emphasis on intensive induction chemotherapy: A report from the Study Group of Japan. Cancer 66:1879–1887, 1990.
2. Tsuchida Y, Yokoyama J, Kaneko M, Uchino J, Iwafuchi M, Makino S, Matsuyama S, Takahashi H, Okabe I, Hashizume K, Hayashi A, Nakada K, Yokoyama S, Nishihira H, Sasaki S, Sawada T, Nagahara N, Okada A: Therapeutic significance of surgery in advanced neuroblastoma: A report from the Study Group of Japan. J Pediatr Surg 27:616–622, 1992.
3. Haase GM, O'Leary M, Ramsay NKC, Romansky SG, Stram DD, Seeger RC, Hammond GD: Aggressive surgery combined with intensive chemotherapy improves survival in poor-risk neuroblastoma. J Pediatr Surg 26:1119–1124, 1991.
4. Grosfeld JL, Baehner RL: Neuroblastoma: An analysis of 160 cases. World J Surg 4:29–38, 1980.
5. LaQuaglia MP, Kushner BH, Heller G, Bonilla MA, Lindsley KL, Cheung N: Stage IV neuroblastoma diagnosed at more than 1 year of age: Gross total resection and clinical outcome. J Pediatr Surg 29:1162–1166, 1994.
6. Nagahara N, Ohkawa H, Suzuki H, Tsuchida Y, Nakajou T: Staging of neuroblastoma. J Clin Oncol 8:179, 1990.
7. Evans AE, D'Angio GJ, Randolph JA: A proposed staging for children with neuroblastoma. Cancer 27:374–378, 1971.
8. Ohnuma N, Takahashi H, Kaneko M, Uchino J, Takeda T, Iwafuchi M, Ohhira M, Nishihira H, Mugishima H, Yokoyama J, Okada A, Nagahara N, Taguchi N, Tsuchida Y: Treatment combined with bone marrow transplantation for advanced neuroblastoma: An analysis of patients who were pre-treated intensively with the protocol of the Study Group of Japan. Med Pediatr Oncol 24:181–187, 1995.
9. Matsumura M, Atkinson JB, Hays DM, Hammond GD, Siegel SE, Sather H, Grosfeld J, Haase G: An evaluation of the role of surgery in metastatic neuroblastoma. J Pediatr Surg 23:448–453, 1988.
10. Paul SR, Tarbell NJ, Korf B, Kretschmar CS, Lavally B, Grier HE: Stage IV neuroblastoma in infants: Long-term survival. Cancer 67:1493–1497, 1991.
11. Tsuchida Y, Honna T, Kamii Y, Asahara S, Sugita K, Taguchi N, Masaki H: Radical excision of primary tumor and lymph nodes in advanced neuroblastoma: Combination with intensive induction chemotherapy. Pediatr Surg Int 6:22–27, 1991.
12. Grosfeld JL: Neuroblastoma in infancy and childhood. In Hays DM (ed): "Pediatric Surgical Oncology." Philadelphia: Grune & Stratton, 1986, pp 63–85.
13. Grosfeld JL, Schatzlein M, Ballantine TUN, Weetman RM, Baehner RL: Metastatic neuroblastoma: Factors influencing survival. J Pediatr Surg 13:59–65, 1978.
14. Shamberger RC, Allarde-Segundo A, Kozakewich HPW, Grier HE: Surgical management of stage III and IV neuroblastoma:

Resection before or after chemotherapy? J Pediatr Surg 26:1113–1118, 1991.

15. Haase GM, Wong KY, deLorimier AA, Sather HN, Hammond GD: Improvement in survival after excision of primary tumor in stage III neuroblastoma. J Pediatr Surg 24:194–200, 1989.
16. Berthold F, Utsch S, Holschneider AM: The impact of preoperative chemotherapy on resectability of primary tumor and complication rate in metastatic neuroblastoma. Z Kinderchir 44:21–24, 1989.
17. Suita S, Zaizen Y, Kaneko M, Uchino J, Takeda T, Iwafuchi M, Utsumi J, Takahashi H, Yokoyama J, Nishihira H, Okada A, Kawa K, Nagahara N, Yano H, Tsuchida Y: What is the benefit of aggressive chemotherapy for advanced neuroblastoma with N-myc amplification? A report from the Japanese Study Group for Treatment of Advanced Neuroblastoma. J Pediatr Surg 29:746–750, 1994.